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Combinatorial Approach to the Discovery of Novel Coordination Complexes

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The relationship of ligand structure to the chemical and physical properties of derived metal complexes is a central theme in such vital and disparate fields as selective catalysis,[1] sensor discovery,[2] and bioinorganic chemistry.[3] The numerous advances made in these fields highlight the utility of complexes with well-designed structural, electronic, and/or stereochemical features. However, the rational design of such complexes remains extremely challenging, especially if novel physical and chemical properties are sought. In this context, a systematic method for the expedient generation of new classes of coordination complexes would clearly be of great value.

The synthesis and screening of combinatorial libraries is a validated strategy for the identification and study of ligand−receptor interactions.[4,5] Combinatorial systems allow many structural changes to be examined simultaneously, thus allowing an evaluation of synergistic effects in ligand binding. Since the stability and activity of metal complexes are similarly dependent on numerous interrelated variables, such as the coordination geometry required by the metal and the steric and electronic characteristics of the ligand, combinatorial chemistry could provide a powerful approach for discovering new types of coordination compounds as well.[6] We outline herein our preliminary results in selective transition metal binding by ligands prepared through solid-phase combinatorial synthesis.

There are two fundamentally different strategies that may be adopted for the design of libraries of potential metal ion binders. One involves attaching a variety of possible binding elements to a known ligand structure. In this context, Still and co-workers recently described the preparation of solid-phase libraries containing cyclen units with short peptidic appendages.[7] Although cyclen is a known tetradentate ligand for metal ions such as Cu(II) and Co(II), these ions were found to bind with selectivity imparted by the variable library elements. This approach may prove particularly useful for the tuning and optimization of properties of known ligands.

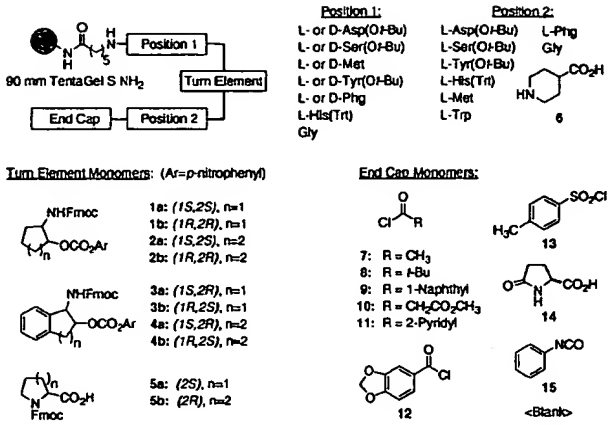


Figure 1. Composition of a turn-element-containing library for the binding of transition metals.

An alternative approach, and the one adopted in the present study, involves the design of libraries of potential ligands without predefined binding sites, but rather with a diverse set of functional groups and conformational restrictions that result in a range of potential coordination environments.

The ligand library comprises four variable components: two amino acids (positions 1 and 2), linked by a "turn element" (**1a,b**−**5a,b**) and terminated by various capping reagents (**7**−**15**) (Figure 1).[8] The turn elements are cyclic 1,2-amino alcohol or α-amino acid derivatives with defined relative and absolute stereochemistry and were introduced with the notion that this conformational restriction would encourage the formation of a potential binding site in which both amino acid side chains might interact with the metal. The ligand library was synthesized on poly(ethylene glycol)-grafted polystyrene (90 mm TentaGel S NH_2 resin) using standard splitting/pooling techniques[9] such that each polymer bead displayed a unique ligand structure. The library, which theoretically consists of 12 000 different ligands, was encoded using established tagging methods.[10]

The potential for members of this library to form coordination complexes was evaluated by exposing samples of the beads to homogeneous solutions of selected metal ions. In a representative experiment, a 10 mg portion of the library (ca. 24 000 beads) was subjected to 0.05 M $Ni(OAc)_2$ in MeOH for 30 min, rinsed with additional MeOH, and air dried. The resulting sample was then treated with a solution of dimethylglyoxime (DMG) in MeOH, a known qualitative test for Ni(II), and the beads were examined under a light microscope. A reddish-pink precipitate was observed to rapidly form and remain trapped in the polymer matrix of about 20% of the beads, confirming the selective incorporation of Ni(II) into some of these ligands (Figure 2A).

In order to ascertain which library members had the highest binding affinity for Ni(II), 10 mg library samples were exposed to solutions of decreasing $Ni(OAc)_2$ concentration in methanol buffered with 0.10 M NaOAc and 0.10 M HOAc.[11] As the concentration was lowered, fewer Ni(II) binders were observed,

(1) (a) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993. (b) *Comprehensive Organometallic Chemistry II*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Hegedus, L. S., Eds.; Pergamon: New York, 1995; Vol. 12.

(2) *Fluorescent Chemosensors for Ion and Molecule Recognition*; Czarnik, A. W., Ed.; ACS Symposium Series 538; American Chemical Society: Washington, DC, 1992.

(3) Lippard, S. J.; Berg, J. M. *Principles of Bioinorganic Chemistry*; University Science Books: Mill Valley, CA, 1994.

(4) For recent reviews on strategies for the synthesis of small-molecule libraries, see: (a) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. (b) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123. (c) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385.

(5) For combinatorial approaches to the study of ligand−receptor interactions, see: (a) Still, W. C. *Acc. Chem. Res.* **1996**, *29*, 155 and references therein. (b) Yu, H.; Chen, J. K.; Feng, S.; Dalgarno, D. C.; Brauer, A. W.; Schreiber, S. L. *Cell* **1994**, *76*, 933. (c) Combs, A. P.; Kapoor, T. M.; Feng, S.; Chen, J. K.; Daudé-Snow, L. F.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 287. (d) Zuckermann, R. N.; et al. *J. Med. Chem.* **1994**, *37*, 2678. (e) Wang, G. T.; Li, S.; Wideburg, N.; Krafft, G. A.; Kempf, D. J. *J. Med. Chem.* **1995**, *38*, 2995. (f) Campbell, D. A.; Bermak, J. C.; Burkoth, T. S.; Patel, D. V. *J. Am. Chem. Soc.* **1995**, *117*, 5381.

(6) Spatially addressed synthetic libraries have been applied with success for the identification of metal-containing solid-state materials (Briceño, G.; Chang, H.; Sun, X.; Schultz, P. G.; Xiang, X.-D. *Science* **1995**, *270*, 273), Tc-binding peptides (Malin, R.; Schneider-Mergenet, J.; et al. *J. Am. Chem. Soc.* **1995**, *117*, 11821), and selective catalysts (Burgess, K.; Lim, H.-J.; Porte, A. M.; Sulikowski, G. A. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 220).

(7) Burger, M. T.; Still, W. C. *J. Org. Chem.* **1995**, *60*, 7382.

(8) Experimental procedures for the synthesis of the library and its components are provided as supporting information.

(9) Furka, A.; Sebestyen, F.; Asgedom, M.; Dibo, G. *Int. J. Pept. Protein Res.* **1991**, *37*, 487.

(10) Ohlmeyer, M. H. J.; Swanson, R. N.; Dillard, L. W.; Reader, J. C.; Asouline, G.; Kobayashi, R.; Wigler, M.; Still, W. C. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 10922.

(11) Equilibration experiments have shown the binding of Ni(II) to be reversible under these conditions.

S0002-7863(96)01842-2 CCC: $12.00

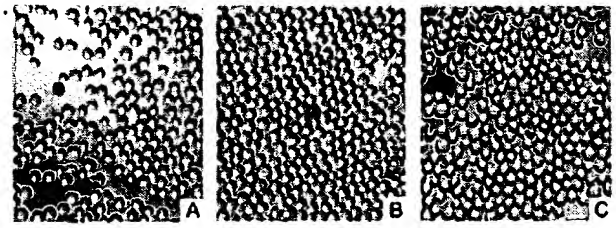


Figure 2. Photographs of metal-containing library samples. (A) Sample containing Ni(II) (red-pink), stained with dimethylglyoxime in MeOH. (B) Sample containing Fe(III) (orange), stained with KSCN in 2% AcOH−MeOH. (C) Sample containing both Ni(II) (blue) and Fe(III) (red-orange), stained with dithiooxamide in THF followed by KSCN in MeOH.

Table 1. Structures of Highest Affinity Ni(II) Binders

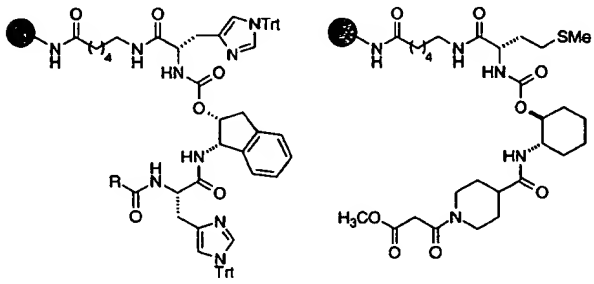
structure	position 1	turn element	position 2	end cap
1, 2	L-His(Trt)	**3a**	L-His(Trt)	**7**
3, 4	L-His(Trt)	**3a**	L-His(Trt)	**9**
5	L-His(Trt)	**2a**	L-His(Trt)	**7**
6	L-His(Trt)	**2a**	L-His(Trt)	**9**

until at a $Ni(OAc)_2$ concentration of 2.5×10^{-4} M only 6 binders out of ~24 000 beads[12] were identified.

Tag photolysis and GC-ECD analysis (Table 1) allowed the identification of these hits and revealed a strong structural consensus among the nickel binders. Four different ligands and two duplicates were found, each bearing L-His(Trt) in both amino acid positions. Furthermore, only two turn elements (**3a** and **2a**) and two end caps (**7** and **9**) were incorporated, suggesting that high-affinity binding does not simply result from the presence of the two histidine residues. The identified structures were confirmed to be Ni(II) binders by independent synthesis of two of the ligands, **16** and **17**, both on solid phase and in solution.[13,14]

The same ligand library is selective in its complexation of other metal ions. Using conditions similar to those described above, Fe(III) complexes were indentified by staining with KSCN in MeOH (Figure 2B). Slightly stronger and less discriminate complexation was observed than with Ni(II), with approximately 1% of the ligands incorporating Fe(III) upon exposure to 5×10^{-4} M $FeCl_3$ and solutions as dilute as 5×10^{-6} M still producing identifiable binders. The structures revealed by tag analysis were found to be very different from those of the Ni(II) binders and displayed a perfect consensus (64/64 structures) for the unexpected combination of isonipecotic acid (**6**) in position 2 followed by end cap **10**. Half of the high-affinity structures were found to contain Met in position 1 (e.g. **18**), but no preference for a particular turn element was apparent.

The fact that there is no structural overlap between binders of Ni(II) and of Fe(III) suggested that the library might selectively bind one metal in the presence of the other. A 10 mg sample of the library was exposed to an equimolar solution of $Ni(OAc)_2$ and $FeCl_3$. After 2 h, the sample was rinsed with MeOH and stained sequentially with dithiooxamide in THF (a stain that forms a blue complex with Ni(II)) and KSCN in MeOH (a stain that forms an orange-red complex with Fe(III)). As can be seen in Figure 2C, selective binding to each metal can be identified.



16 R = CH_3
17 R = 1-naphthyl

18

Binding of other ions to the library was also observed, albeit with varying degrees of selectivity. Cu(II) bound to ~30% of the beads, with a marked preference for members containing L-His(Trt). Pt(IV) was also found to complex with up to 30% of the ligands, the majority of which contained a Met residue. Sn(IV) and Pd(II) were observed to bind with little-to-no selectivity, suggesting that complexation of these ions might occur solely through the peptide backbone.[15]

In conclusion, we have demonstrated that combinatorial libraries can be successfully applied to the discovery of novel metal−ligand complexes. The structural information thus obtained has revealed unanticipated and nonintuitive structural effects in binding selectivity and affinity. The investigation of the properties and applications of the coordination complexes uncovered by this approach is being actively pursued in our laboratories and will be reported in due course.

Acknowledgment. This work was supported by a generous gift from Versicor, Inc. We thank Prof. S. L. Schreiber and his research group for helpful discussions and valuable experimental advice. Predoctoral fellowship support to M.B.F. (NSF) and postdoctoral fellowship support to N.S.F. (NIGMS) are gratefully acknowledged.

Supporting Information Available: Experimental details and full characterization of intermediates pertaining to both the solid and solution phase synthesis of metal binders; consensus binding data for Pt(IV), Sn(IV), Cu(II), and Pd(II) (8 pages). See any current masthead page for ordering and Internet access instructions.

JA961842U

(12) A sample of 24 000 beads, or 2.0 copies of the library, assures that 95% of the ligands are represented with 99% confidence. Burgess, K.; Liaw, A. I.; Wang, N. *J. Med. Chem.* **1994**, *37*, 2985.

(13) Binding experiments carried out three times using $[Ni(OAc)_2] = 2.5 \times 10^{-4}$ M and at a variety of higher Ni concentrations led to the identification of **16** and **17** as ligands in every case.

(14) For both **16**·Ni and **17**·Ni, the predominant species corresponds to a 1:1 complex of Ni(II) and doubly-deprotonated ligand ($Ni{\cdot}LH_{n-2}$). Several other hits from this binding screen have been resynthesized on solid phase for binding confirmation. Experiments to determine the association constants of these complexes are underway and will be reported separately.

(15) In all cases, control experiments revealed no detectable metal ion binding to the poly(ethylene glycol) support. The structures of representative ligands for each of these metals are provided in the supporting information.

Part I. Monomer Synthesis and Characterization.

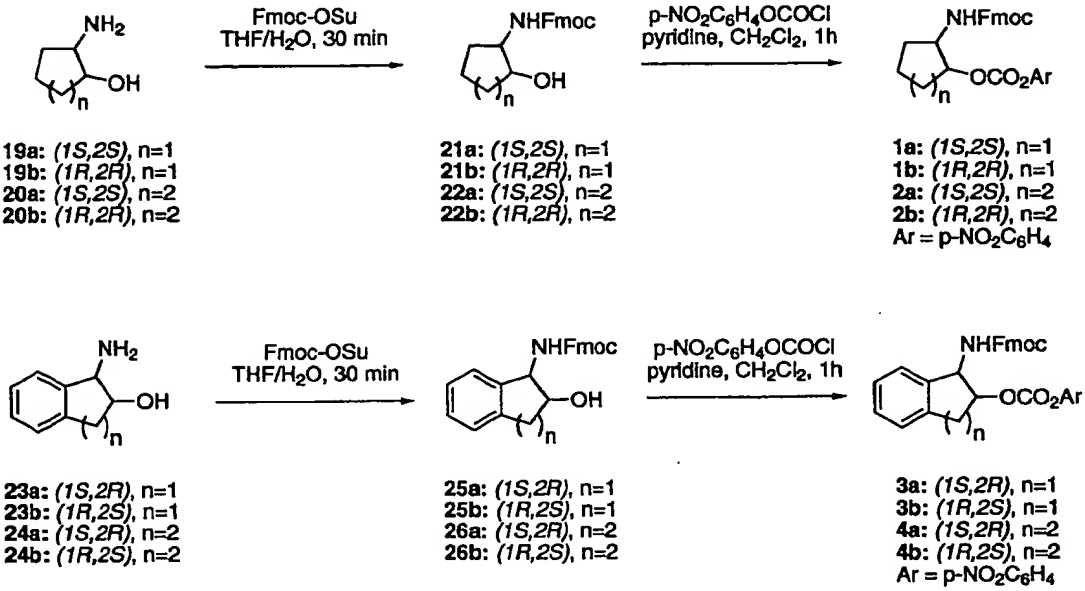


Figure S1. Synthesis of turn element monomers.

Fmoc-protection of 1,2-amino alcohols: All 8 amino alcohols were protected using the representative procedure listed below. Full spectral characterization is listed for the **a** series.

Fmoc-amino alcohol 25a: To a stirred solution of 1.0 g (6.7 mmol) of **23a** in 33 mL of 10:1 THF/H_2O were added 2.25 g (6.7 mmol) of succinimidyl 9-fluorenylmethyl carbonate. The resulting solution was stirred at ambient temperature for 30 min and then partitioned between 100 mL of CH_2Cl_2 and 50 mL of aqueous 1 M $NaHSO_4$. The organic phase was washed with three 50-mL portions of distilled water, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was dissolved in 5 mL of CH_2Cl_2 and precipitated by the slow addition of 50 mL of hexanes, yielding 2.37 g (6.4 mmol, 96%) of **25a** as a white amorphous solid: IR (thin film) 3421 (br), 3065, 2940, 1693, 1529, 1450, 1249 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 7.5 Hz, 2H), 7.63 (d, J = 7.3 Hz, 2H), 7.42 (t, J = 7.5 Hz, 2H), 7.33 (t, J = 7.4 Hz, 2H), 7.24 (br s, 4H), 5.41 (m, 1H), 5.14 (m, 1H), 4.60 (m, 1H), 4.54 (m, 2H), 4.27 (t, J = 6.6 Hz, 1H), 3.14 (dd, J = 4.5, 16.3 Hz, 1H), 2.93 (d, J = 16.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 143.8, 141.3, 139.7, 128.3, 128.2, 127.7, 127.2, 127.1, 125.4, 125.0, 124.4, 120.0, 73.5, 66.8, 59.2, 47.3, 25.3.

Fmoc-amino alcohol 21a: The product was prepared and isolated as described above in 70% yield: IR (thin film) 3323 (br), 2959, 1688, 1541, 1448, 1240 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 7.5 Hz, 2H), 7.59 (d, J = 7.3 Hz, 2H), 7.41 (t, J = 7.5 Hz, 2H), 7.34 (t, J = 7.4 Hz, 2H), 4.87 (br s, 1H), 4.45 (m, 2H), 4.21 (t, J = 6.6 Hz, 1H), 4.21 (m, 1H), 3.72 (m, 1H), 2.18 (m, 1H), 2.09 (m, 1H), 1.82 (m, 1H), 1.75 (m, 2H), 1.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 143.8, 141.3, 128.2, 127.7, 127.4, 127.0, 125.2, 125.0, 124.9, 120.0, 79.5, 66.8, 60.8, 47.2, 32.4, 30.5, 20.9.

Fmoc-amino alcohol 22a: The product was prepared and isolated as described above in 75% yield: IR (thin film) 3323, 2939, 2866, 1686, 1543, 1449, 1316, 1258 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 7.5 Hz, 2H), 7.59 (d, J = 7.3 Hz, 2H), 7.41 (t, J = 7.5 Hz, 2H), 7.34 (t, J = 7.4 Hz, 2H), 4.87 (br s, 1H), 4.45 (m, 2H), 4.35 (t, J = 6.6 Hz, 1H), 3.40 (m, 2H), 2.05 (m, 2H), 1.75 (m, 2H), 1.25 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 127.7, 127.0, 124.9, 120.0, 66.8, 47.2, 24.6, 24.0.

Fmoc-amino alcohol 26a: The product was prepared and isolated as described above in 76% yield: IR (thin film) 3318 (br), 3067, 2947, 1680, 1537, 1257 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 7.5 Hz, 2H), 7.61 (d, J = 7.3 Hz, 2H), 7.41 (t, J = 7.5 Hz, 2H), 7.32 (t, J = 7.4 Hz, 2H), 7.21 (m, 3H), 7.12 (m, 1H), 5.21 (d, J = 8.3 Hz, 1H), 4.95 (m, 1H), 4.51 (m, 2 H), 4.25 (t, J = 6.7 Hz, 1H), 4.18 (m, 1H), 2.97 (m, 1H), 2.78 (m, 1H), 2.4 (br s, 1H), 1.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 143.8, 143.7, 141.3, 136.2, 134.4, 129.0, 128.7, 127.7, 127.1, 126.6, 125.0, 120.0, 68.9, 66.9, 53.4, 47.3, 27.0, 25.6.

Preparation of 4-nitrophenyl carbonates: Monomers **1a,b - 4a,b** were prepared using the representative procedure described below. Full spectral characterization is listed for the a series.

4-Nitrophenyl carbonate 3a: To a solution of **25a** (0.12 g, 0.31 mmol) in CH_2Cl_2 (10 mL) were added sequentially pyridine (0.05 mL, 0.63 mmol) and 4-nitrophenyl chloroformate (0.08 g, 0.39 mmol). The solution was stirred under N_2 at room temperature until the starting material was consumed (1 hr), at which point the reaction mixture was concentrated to a yellow oil. Purification by silica gel chromatography (2% EtOAc/CH_2Cl_2) afforded **3a** as a white solid (0.14 g, 0.25 mmol, 81% yield): IR (thin film) 3310, 1767, 1716, 1524, 1326, 1257, 1210 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 7.3 Hz, 2H), 7.62 (d, J = 7.5 Hz, 2H), 7.38 (t, J = 7.4 Hz, 2H), 7.30 (m, 8H), 5.59 (m, 1H), 5.50 (m, 1H), 5.25 (d, J = 7.16 Hz, 1H), 4.65 (m, 1H), 4.55 (m, 1H), 4.30 (m, 1H), 3.32 (dd, J = 5.0, 17.5 Hz, 1H), 3.23 (d, J = 18.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 155.3, 151.9, 143.7, 141.4, 141.3, 138.5, 128.9, 127.8, 127.7, 127.1, 125.3, 125.2, 125.0, 124.9, 124.0, 121.6, 120.0, 67.1, 57.6, 47.3, 36.8; MS *m/z* ($M-Na^+$) calcd 559.1481, obsd 559.1499.

4-Nitrophenyl carbonate 1a: The product was prepared and isolated as described above in 96% yield: IR (thin film) 3410, 3380, 3067, 2971, 2876, 1766, 1722, 1525, 1347, 1259, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, J = 6.7, 1.8 Hz, 2H), 7.76 (dd, J = 6.7, 1.8 Hz, 2H), 7.62 (m, 2H), 7.35 (m, 6H), 5.07 (m, 2H), 4.42 (m, 2H), 4.15 (m, 2H), 2.17 (m, 2H), 1.82 (m, 3H), 1.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 155.4, 152.1, 145.2, 143.7, 142.3, 141.2, 128.1, 127.6, 127.0, 125.1, 124.9, 121.7, 120.1, 119.9, 84.6, 72.8, 66.7, 60.3, 57.4, 47.1, 46.2, 30.2, 29.7, 25.3, 20.8, 14.1; MS *m/z* ($M-Na^+$) calcd 511.1481, obsd 511.1499.

4-Nitrophenyl carbonate 2a: The product was prepared and isolated as described above in 70% yield: IR (thin film) 2834, 2859, 1761, 1709, 1525, 1266, 1211 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.4 Hz, 2H), 7.77 (m, 2H), 7.57 (d, J = 7.3 Hz, 2H), 7.53 (d, J = 7.2 Hz, 2H), 7.40 (m, 2H), 7.3 (m, 2H), 4.87 (m, 1H), 4.62 (m, 1H), 4.37 (m, 2H), 4.18 (m, 1H), 3.78 (m, 1H), 2.3 (m, 2H), 1.85 (m, 1H), 1.70 (m, 1H), 1.61 (m, 1H), 1.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 155.3, 143.8, 141.3, 127.8, 127.1, 125.2, 125.0, 124.9, 121.6, 120.0, 66.9, 54.2, 47.2, 32.2, 30.7, 24.1, 23.8; MS *m/z* (M^+-Na) calcd 525.1638, obsd 525.1643.

4-Nitrophenyl carbonate 4a: The product was prepared and isolated as described above in 76% yield: IR (thin film) 3424, 3289, 2950, 1768, 1718, 1522, 1260, 1227, 1209, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 7.5 Hz, 2H), 7.78 (d, J = 7.5 Hz, 2H), 7.35 (m, 12H), 5.27 (m, 3H), 4.50 (m, 2H), 4.26 (t, J = 6.6 Hz, 1H), 2.97 (m, 2H), 2.10-2.40 (m, 2H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 155.5, 151.9, 145.3, 143.9, 143.6, 141.3, 135.5, 133.3, 129.0, 128.7, 128.0, 127.7, 127.0, 126.9, 126.8, 125.17, 124.9, 121.8, 120.0, 119.9, 76.4, 66.8, 60.3, 50.6, 47.2, 29.6, 25.8, 23.9, 14.1; MS *m/z* ($M-Na^+$) calcd 573.1638, obsd 573.1644.

Part II. S lid Phas Library Synthesis.

General: 90 μm TentaGel S NH_2 resin (0.23 mmol/g loading) was obtained from Rapp Polymere and derivatized with 6-aminocaproic acid using procedures c and e (Figure S2). All coupling reacti ns were carried out in fritted 1.5 mL disposable chromatography columns and terminated via filtration, followed by thorough rinsing with DMF, MeOH, CH_2Cl_2, and hexanes. The progress of all amino acid and 4-nitrophenyl carbonate coupling reactions (steps c and **f**) was monitored by the UV quantification of dibenzofulvene released by 5 mg resin samples upon Fmoc cleavage. End capping reactions (step **g**) were continued until resin samples gave a negative Kaiser test.[1]

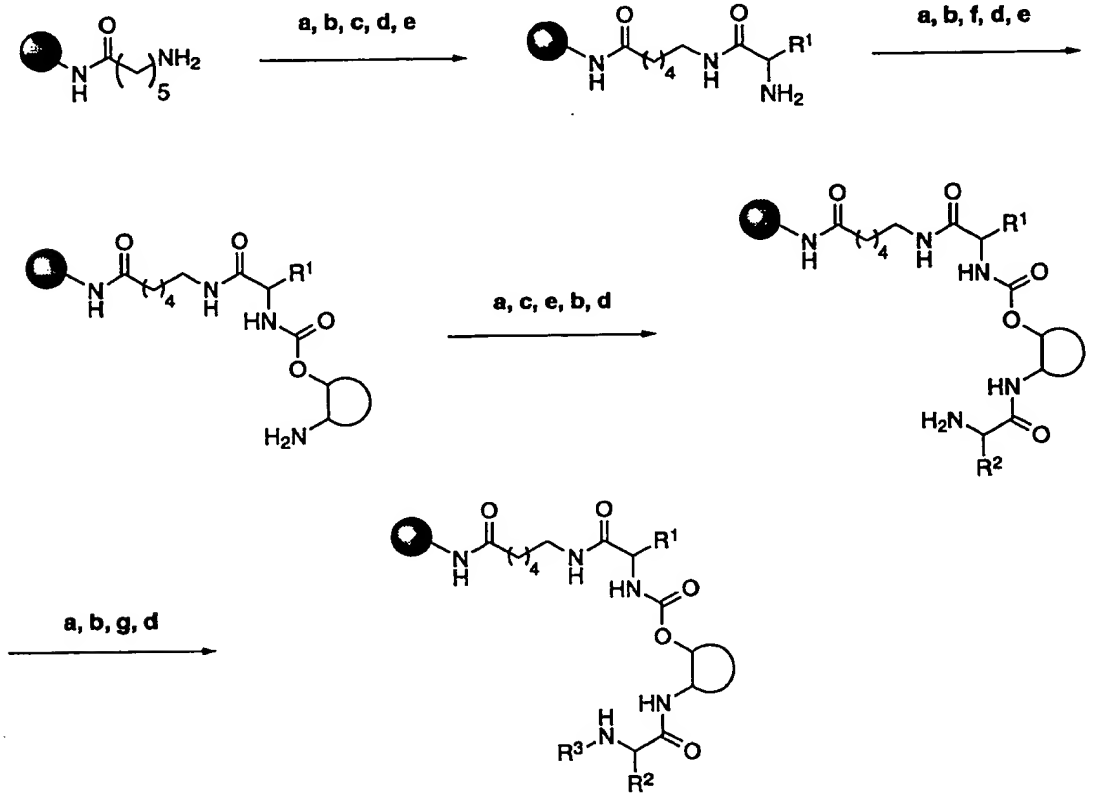


Figure S2. Synthesis outline for the turn-element containing library: (**a**) The library was split into the appropriate number of vials. (**b**) 3 mol % tag acid[2], 50 eq DIC, 50 eq HOBT, CH_2Cl_2, 12 h. (**c**) 5 eq Fmoc-amino acid, 5 eq HBTU, 10 eq DIPEA, 5 eq HOBT, DMF, 2 h. (**d**) The individual library vials were pooled. (**e**) 50% piperidine in DMF, 30 min. (**f**) For monomers **1a,b - 4a,b**: 5 eq 4-nitrophenyl carbonate, 5 eq HOBT, 2.5 eq DIPEA, NMP, 4 h.[3] For Fmoc-amino acids **5a** and **5b**: see **c**, above. (**g**) For monomers **7 - 11** and **14**: 10 eq acid or sulfonyl chloride, 5 eq DMAP (for acid chlorides only), 25 eq DIPEA, dichloroethane, 2.5 h. For acids **12** and **13**: see **c**, above. For isocyanate **15**: 10 eq PhNCO, 10 eq DIPEA, NMP, 2.5 h.

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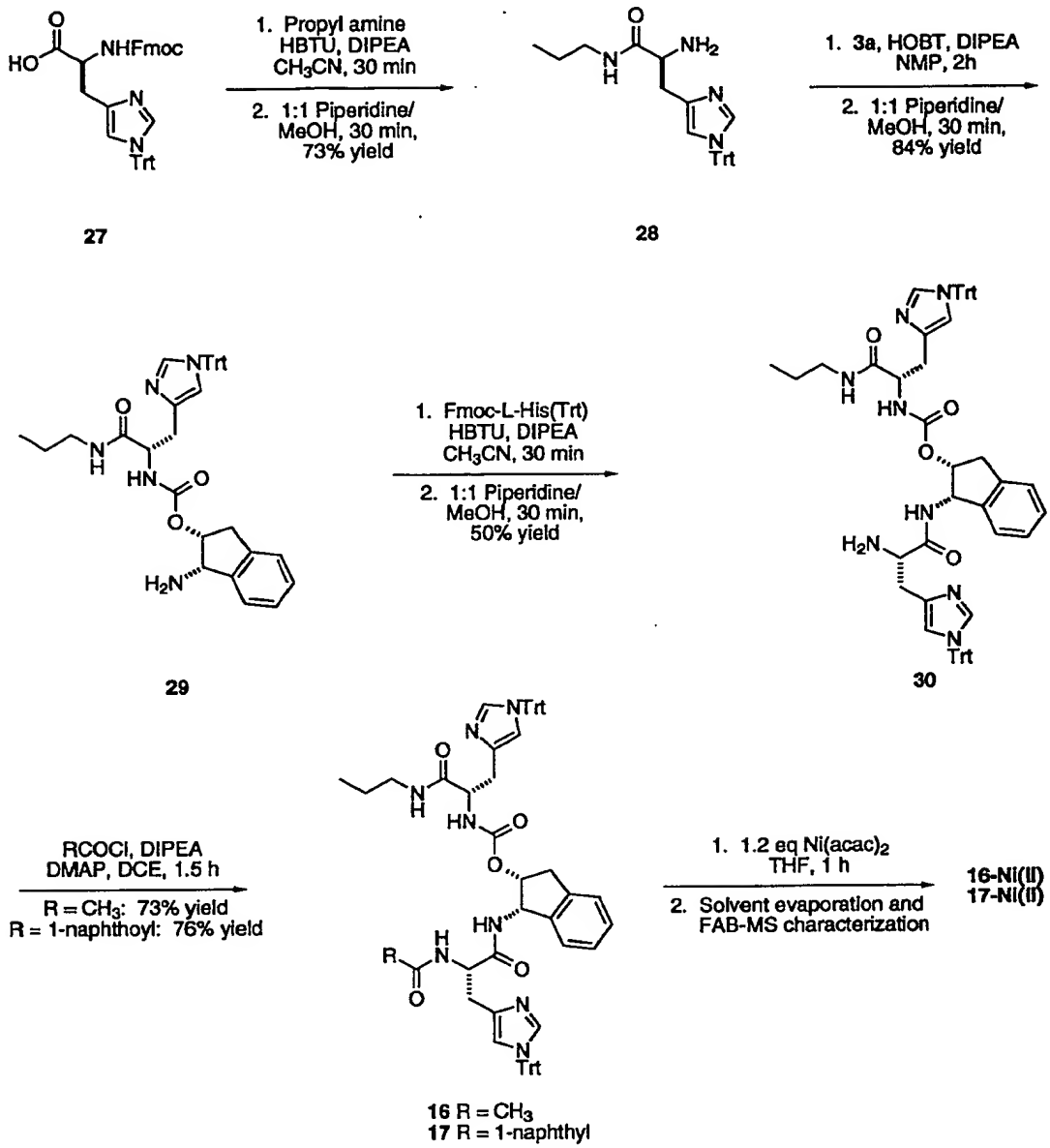
[1] Kaiser, E. et al. *Anal. Biochem.* **1970**, *34*, 595.
[2] Ohlmeyer, M. H. J.; Swanson, R. N.; Dillard, L. W.; Reader, J. C.; Asouline, G.; Kobayashi, R.; Wigler, M.; Still, W. C. *Proc. Nat. Acad. Sci. U.S.A.* **1993**, *90*, 10922.
[3] Cho, C. Y.; Moran, E. J.; Cherry, S. R.; Stephans, J. C.; Fodor, S. P. A.; Adams, C. L.; Sundaram, A.; Jacobs, J. W.; Schultz, P. G. *Science* **1993**, *261*, 1303.

Part III. Soluti n Phas Synthesis f Two Ni(II) Binders.



27 **28** **29** **30**

16 R = CH_3
17 R = 1-naphthyl

Amine 28: To a suspension of 750 mg of FmocHis(Trt) (1.21 mmol) and 0.49 mL (2.66 mmol) of i-Pr_2NEt in 10 mL of CH_3CN were added 504 mg of 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU, 1.33 mmol). The suspension became homogeneous after 2 min, and then 143 mg of propylamine (2.42 mmol) were added. After 30 min, the reaction mixture was partitioned between 50 mL of $CHCl_3$ and 50 mL of H_2O, and the organic phase was extracted with two 50-mL portions of water, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was passed through a short plug of silica (to remove amine impurities) with 3% MeOH/CH_2Cl_2. ^{1}H NMR analysis of the crude product mixture after concentration indicated the presence of the desired product and tetramethyl urea. The residue was dissolved in 10 mL of 1:1 piperidine/MeOH, stirred for 30 min, and partitioned between 50 mL of $CHCl_3$ and 25 mL of H_2O. The organic phase was extracted with three 25-mL portions of H_2O, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by silica gel chromatography (5%

MeOH/CH_2Cl_2) afforded 385 mg (73% yield, 2 steps) f the desired amine **28** as a colorless oil: IR (thin film) 3360, 3306, 3061, 2962, 2932, 1660, 1492, 1446 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (m, 1H), 7.35 (s, 1H), 7.32 (m, 9H), 7.10 (m, 6H), 6.64 (s, 1H), 3.60 (m, 1H), 3.16 (m, 2H), 3.01 (dd, *J* = 3.3, 11.6 Hz, 1H), 2.74 (dd, *J* = 6.5, 11.6 Hz, 1H), 1.93 (br s, 2H), 1.46 (q, *J* = 5.9 Hz, 2H), 0.88 (t, *J* = 5.9 Hz, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 142.4, 138.5, 138.2, 129.7, 128.0, 119.4, 75.2, 55.7, 40.7, 33.2, 22.8, 11.3; MS *m/z* (M^+-Na) calcd 461.2317, obsd 461.2320.

Amine 29: To a solution of 100 mg of **28** (0.23 mmol), 0.020 mL of i-Pr_2NEt (0.11 mmol), and 31 mg of *N*-hydroxybenzotriazole (HOBT, 0.23 mmol) in 2.5 mL of *N*-methylpyrrolidinone were added 123 mg (0.23 mmol) of **3a**. After 2 h of stirring, the resulting yellow solution was partitioned between 50 mL of EtOAc and 25 mL of H_2O. The organic phase was extracted with three 25-mL portions of water, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was dissolved in 10 mL of 1:1 piperidine/MeOH, stirred for 30 min, and partitioned between 50 mL of CH_2Cl_2 and 25 mL of water. The organic phase was extracted with three 25-mL portions of water, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the residue via silica gel chromatography (5% MeOH/CH_2Cl_2) yielded 119 mg (84% yield, 2 steps) of the desired amine as a colorless foam: IR (thin film) 3306, 3062, 2963, 1713, 1661, 1537, 1244 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (m, 1H), 7.32 (m, 11H), 7.24 (m, 2H), 7.08 (m, 7H), 6.64 (br s, 2H), 5.40 (m, 1H), 4.49 (m, 1H), 4.44 (m, 1H), 3.12 (m, 4H), 3.00 (d, *J* = 17.0 Hz, 1H), 2.88 (dd, J = 6.1, 14.5 Hz, 1H), 2.0 (br s, 2H), 1.42 (q, *J* = 7.2 Hz, 2H), 0.84 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 156.1, 143.8, 142.2, 139.4, 138.3, 136.7, 129.6, 128.0, 127.9, 127.7, 127.0, 124.7, 123.9, 119.5, 77.7, 75.2, 59.0, 54.9, 41.0, 36.9, 30.4, 22.7, 11.3; MS *m/z* (M^+-Na) calcd 636.2887, obsd 636.2953.

Amine 30: To a stirred suspension of 119 mg of amine **29** (0.19 mmol), 120 mg of FmocHis(Trt) (0.19 mmol), 26 mg of *N*-hydroxybenzotriazole (HOBT, 0.19 mmol), and 0.075 mL of i-Pr_2NEt (0.39 mmol) were added 73 mg of 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU, 0.19 mmol). After 8h, the resulting homogeneous solution was partitioned between 25 mL of $CHCl_3$ and 25 mL of water. The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Amine impurities were removed by eluting the product mixture through a plug of silica. A ^1H NMR spectrum of the concentrated product mixture was consistent with the desired product contaminated with tetramethylurea. The mixture was dissolved in 10 mL of 1:1 piperidine/MeOH, stirred for 30 min, and partitioned between 25 mL of $CHCl_3$ and 25 mL of water. The organic layer was rinsed with three 25-mL portions of distilled water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification via silica gel chromatography (5% MeOH/CH_2Cl_2) afforded 96 mg (50% yield, 2 steps) of amine **30** as a colorless foam: IR (thin film) 3338 (br), 3063, 2963, 1722, 1660, 1516, 1446, 1238, 910 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.6 Hz, 1H), 7.26 (m, 20H), 7.17 (m, 4H), 7.05 (m, 13H), 6.68 (s, 1H), 6.61 (br s, 2H), 5.55 (m, 1H), 5.47 (m, 1H), 4.40 (m, 1H), 3.67 (m, 1H), 3.05 (m, 6H), 2.8 (m, 2H), 1.39 (q, *J* = 6.8 Hz, 2H), 0.76 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 171.0, 155.6, 142.4, 142.3, 140.5, 139.7, 138.5, 138.4, 137.9, 136.8, 129.7, 128.2, 128.0, 127.2, 124.9, 119.5, 119.4, 109.9, 104.7, 75.5, 75.2, 55.6, 55.1, 43.4, 40.1, 38.5, 38.3, 36.7, 33.3, 22.7, 11.4; MS *m/z* (M-Na^+) calcd 1015.4635, obsd 1015.4602.

Ligand 16: To a stirred solution of 25 mg (0.025 mmol) of **30**, 1.5 mg (0.013 mmol) of *N,N*-dimethylaminopyridine, and 0.050 mL (0.29 mmol) of i-Pr_2NEt in 1.5 mL of dichloroethane were added 10 μL of acetyl chloride (0.140 mmol). The reaction mixture was stirred for 1 h and then partitioned between 25 mL of CH_2Cl_2 and 25 mL of dilute aqueous Na_2CO_3. The organic layer dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification via silica gel chromatography (5% MeOH/CH_2Cl_2) yielded 19 mg (73% yield) of **16** as a glassy colorless solid: IR (thin film) 3295 (br), 3061, 2965, 1724, 1659, 1532, 1447, 1240, 910 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 6.5 Hz, 1H), 7.69 (t, *J* = 5.6 Hz, 1H), 7.33 (s, 1H), 7.29 (m, 18H), 7.17 (m, 2H), 7.01 (m, 14H), 6.93 (m, 1H), 6.90 (d, *J* = 7.5 Hz, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 6.76 (s, 1H), 6.62 (s, 1H), 5.50 (d, *J* = 6.5 Hz, 1H), 4.60 (q, *J* = 6.0 Hz, 1H), 4.44 (q, *J* = 3.1 Hz, 1H), 3.20 (dd, *J* = 4.8, 14.8 Hz, 1H), 3.13 (dd, *J* = 4.8,15.5 Hz, 1H), 3.11 (m, 1H), 3.09 (q, *J* = 6.8 Hz, 2H), 2.97 (d, *J* = 17.1 Hz, 1H), 2.88 (dd, *J* = 5.4, 14.8 Hz, 1H), 2.82 (dd, *J* = 4.8, 14.6 Hz, 1H), 1.84 (s, 3H), 1.40 (q, *J* = 7.3 Hz, 2H), 0.78 (t, *J* = 7.3 Hz), 3H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 171.7, 171.5, 170.5, 155.4, 143.3, 142.3, 142.2, 139.1, 139.6, 138.4, 138.3, 135.5, 134.9, 129.7, 129.6, 128.1, 128.0, 127.9, 126.9, 125.0, 123.6, 120.0, 119.7, 110.0, 75.6, 75.3, 75.2, 55.5, 55.4, 41.2, 37.8, 35.5, 33.5, 28.5, 23.2, 22.7, 11.4; MS *m/z* (M^+-Na) 1057.

Ligand 17: To a stirred solution of 25 mg (0.025 mmol) of **30**, 1.5 mg (0.013 mmol) of *N,N*-dimethylaminopyridine, and 0.050 mL (0.29 mmol) of i-Pr_2NEt in 1.5 mL of dichloroethane were added 10 μl of 1-naphthoyl chloride (0.066 mmol). The reaction mixture was stirred for 1 h and then partitioned between 25 mL of CH_2Cl_2 and 25 mL of dilute aqueous Na_2CO_3. The organic layer dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification via silica gel chromatography (5% MeOH/CH_2Cl_2) yielded 22 mg (76% yield) of **17** as a glassy colorless solid: IR (thin film) 3306 (br), 3059, 2963, 1722, 1657, 1527, 1446, 1238, 908 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J* = 6.7 Hz, 1H), 8.12 (d, *J* = 8.5 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 6.5 Hz, 1H), 7.25 (m, 24H), 7.09 (m, 12H), 6.89 (m, 4H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.80 (s, 1H), 6.46 (s, 1H), 5.64 (m, 1H), 5.53 (dd, *J* = 5.6, 8.5 Hz, 1H), 4.95 (q, *J* = 6.1 Hz, 1H), 4.44 (m, 1H), 3.30 (dd, *J* = 5.5, 14.8 Hz, 1H), 3.16 (dd, *J* = 5.4, 16.5 Hz, 1H), 3.08 (dd, *J* = 5.5, 14.9 Hz, 1H), 3.01 (dd, *J* = 2.3, 16.8 Hz, 1H), 2.95 (dd, *J* = 5.5, 14.8 Hz, 1H), 2.91 (q, *J* = 6.4 Hz, 2H), 2.80 (dd, *J* = 4.7, 14.6 Hz, 1H), 1.20 (q, *J* = 7.3 Hz, 2H), 0.60 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 171.0, 170.0, 155.6, 142.3, 142.2, 140.5, 139.8, 138.4, 138.2, 136.8, 133.7, 133.4, 130.7, 130.1, 129.6, 129.5, 128.2, 128.1, 128.0, 127.8, 127.1, 126.3, 125.3, 125.0, 124.9, 124.6, 124.0, 120.0, 119.3, 75.4, 75.3, 55.7, 55.5, 41.0, 40.1, 37.3, 35.0, 30.7, 29.0, 22.6, 11.2 ; MS *m/z* (M^+-Na) 1169.

Ni(II) complex 16-Ni: 3 mg of **16** (0.003 mmol) were dissolved 0.5 mL of a 0.01 M Ni(acac)$_2$ solution (1.7 eq) in THF. After 30 min the green solution was concentrated under a stream of N_2 and submitted for FAB-MS analysis: *m/z* (M^+-H) 1091, corresponding to M = Ni•LH_{n-2}. No unbound ligand or 2:1 metal-ligand complexes were observed.

Ni(II) complex 17-Ni: 3 mg of **17** (0.003 mmol) were dissolved 0.5 mL of a 0.01 M Ni(acac)$_2$ solution (1.7 eq) in THF. After 30 min the green solution was concentrated under a stream of N_2 and submitted for FAB-MS analysis: *m/z* (M^+-H) 1202, corresponding to M = Ni•LH_{n-2}. A minor amount of unbound ligand (*m/z* (M^+-Na) 1169) was also observed.

Part IV. Representativ Binders for Other Metals.

Table S1: Representative Fe(III) binders.[a]

Structure	Amino Acid 1	Turn Element	Amino Acid 2	End Cap
1	D-Asp(O^{t}Bu)	**4b**	**6**	**11**
2	D-Ser(O^{t}Bu)	**3b**	**6**	**11**
3	D-Ser(O^{t}Bu)	**3a**	**6**	**11**
4	L-Tyr(O^{t}Bu)	**2b**	**6**	**11**
5	L-Tyr(O^{t}Bu)	**4b**	**6**	**11**
6	D-Tyr(O^{t}Bu)	**5b**	**6**	**11**
7	Gly	**1b**	**6**	**11**
8	L-Met	**5b**	**6**	**11**
9	L-Met	**5b**	**6**	**11**
10	L-Met	**4b**	**6**	**11**
11	D-Met	**4b**	**6**	**11**
12	D-Met	**4b**	**6**	**11**
13	D-Met	**3a**	**6**	**11**
14	D-Met	**1a**	**6**	**11**

[a]A 10 mg sample of library was exposed to 10 ml of a 5 x 10^{-6} M $FeCl_3$ solution in 0.1 M HOAc, 0.1 M NaOAc, MeOH for 12 h. The resin was isolated via filtration and rinsed thoroughly with MeOH. Red-orange Fe(III) binders were identified using a 10 mg/mL solution of KSCN in 2% HOAc/MeOH.

Table S2. Representative Pt(IV) binders.[a]

Structure	Amino Acid 1	Turn Element	Amino Acid 2	End Cap
1	L-Met	**2a**	L-Met	**13**
2	L-Met	**5a**	**6**	**9**
3	D-Met	**2b**	Gly	**10**
4	L-Met	**5b**	L-Met	<Blank>
5	D-Met	**1b**	**6**	<Blank>
6	L-Met	**5a**	**6**	**11**

[a]A 10 mg sample of library was exposed to 10 ml of a 5 x 10^{-4} M H_2PtCl_6 solution in 0.1 M HOAc, 0.1 M NaOAc, MeOH for 12 h. The resin was isolated via filtration and rinsed thoroughly with MeOH. About 30% of the beads turned bright red upon treatment with a dilute solution of dithiooxamide in MeOH, confirming the presence of Pt(IV).

Table S3. Representative ligands for Cu(II).[a]

Structure	Amino Acid 1	Turn Element	Amino Acid 2	End Cap
1	L-His(Trt)	**3a**	L-His(Trt)	**9**
2	L-His(Trt)	**4a**	L-His(Trt)	**12**
3	L-His(Trt)	**3b**	L-His(Trt)	**12**
4	L-His(Trt)	**3a**	L-His(Trt)	<Blank>
5	L-His(Trt)	**1a**	L-His(Trt)	<Blank>
6	L-His(Trt)	**2a**	<Blank>	<Blank>
7	D-Phg	**1b**	L-Trp	**12**
8	D-Phg	**4b**	L-Trp	**12**
9	Gly	**1a**	Gly	**12**

[a]A 10 mg sample of library was exposed to 10 ml of a 5 x 10^{-4} M $Cu(OAc)_2$ solution in 0.1 M HOAc, 0.1 M NaOAc, MeOH for 12 h. The resin was isolated via filtration and rinsed thoroughly with MeOH. Dark green Cu(II) binders (c. 30% of the library) were identified by staining the resin with a dilute solution of dithiooxamide in MeOH.

Table S4. Sample Sn(IV) binders.[a]

Structure	Amino Acid 1	Turn Element	Amino Acid 2	End Cap
1	D-Met	3b	L-His(Trt)	10
2	L-Met	3b	L-Phg	10
3	L-Tyr(O^{t}Bu)	3b	L-Tyr(O^{t}Bu)	8
4	L-Tyr(O^{t}Bu)	4a	L-Asp(O^{t}Bu)	8
5	L-Phg	3a	L-Tyr(O^{t}Bu)	<Blank>

[a]A 10 mg sample of library was exposed to 10 ml of a 5 x 10^{-4} M $Sn(OAc)_4$ solution in 0.1 M HOAc, 0.1 M NaOAc, MeOH for 12 h. The resin was isolated via filtration and rinsed thoroughly with MeOH. Purple to brown Sn(IV) binders were identified (c. 50% of the library) by staining the resin with a dilute solution of pyrocatechol violet in MeOH.

Table S5. Sample ligands for Pd(II).[a]

Structure	Amino Acid 1	Turn Element	Amino Acid 2	End Cap
1	D-Asp(O^{t}Bu)	3a	L-Met	9
2	L-Phg	1a	L-Ser(O^{t}Bu)	11
3	D-Met	1b	L-Trp	<Blank>
4	D-Phg	1a	L-Phg	12
5	Gly	1a	L-Trp	12

[a]A 10 mg sample of library was exposed to 10 ml of a 5 x 10^{-4} M $Pd(OAc)_2$ solution in 0.1 M HOAc, 0.1 M NaOAc, MeOH for 12 h. The resin was filtered and rinsed thoroughly with MeOH. Brown Pd(II) binders could be identified without further staining (c. 90% of the library).